Scientific reviews

MORPHOLOGICAL CHANGES IN HEMATOPOIETIC PARAMETERS IN COVID-19 AND THEIR PROGNOSTIC SIGNIFICANCE

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Resume. *The types of morphological changes in the complete blood count, along with other laboratory parameters, can help establish the severity of the condition and provide the prognostic value in determining the survival of a patient with COVID-19. Peripheral blood smear (PBS) examination is a routine and simple procedure that can be performed at any medical institution. However, data on morphological changes in PBS during COVID-19 are still insufficient. Therefore, it is relevant to identify the features and patterns of these changes, taking into account the severity of the clinical presentation of COVID-19, and establish their prognostic significance.*
The aim. *To review the literature on the presence of morphological changes in hematopoietic parameters in the case of SARS-CoV-2 infection with respect to the disease course.*
Results and Conclusions. *Morphological changes in at least one blood cell lineage were observed in all cases of SARS-CoV-2 infection. The most common are nuclear and cytoplasmic disorders of neutrophils, such as hypogranulation and hypo/hypersegmentation of neutrophil nuclei, often with toxogenic stippling. Typical changes in lymphocyte morphology include monocytoid, lymphoplasmacytoid, granular, and atypical cells with nucleoli. Prognostically unfavorable morphological signs in the PBS include giant neutrophils and their toxic granulation, plasmacytization of lymphocytes, and a dynamic decrease in granular and abnormal lymphocytes and monocytes. A low count of lymphocytes and their subpopulations is associated with a severe clinical presentation and an unfavorable outcome of COVID-19 disease, which suggests the feasibility of their immunophenotypic evaluation and monitoring. The detection and serial monitoring of inflammatory monocytes using flow cytometry may be valuable in predicting the course and choosing adequate therapy for SARS-CoV-2 infection. Additionally, an increase in the red cell distribution width was also shown to have prognostic importance.*

МОРФОЛОГІЧНІ ЗМІНИ ПОКАЗНИКІВ КРОВОТВОРЕННЯ ПРИ COVID-19 ТА ЇХ ПРОГНОСТИЧНЕ ЗНАЧЕННЯ

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Резюме. *Види морфологічних змін загального аналізу крові разом з іншими лабораторними показниками можуть допомогти встановити тяжкість стану та надати прогностичну інформацію при визначенні виживаності пацієнта з COVID-19. Дослідження мазка периферичної крові – рутинна і проста процедура, яку можна виконати в будь-якому медичному закладі. Проте даних про морфологічні зміни в периферичному мазку крові під час COVID-19 ще недостатньо. Тому актуальним є виявлення особливостей і закономірностей цих змін з урахуванням тяжкості клінічної картини COVID-19 та встановлення їх прогностичної значущості.*
Мета дослідження – *провести огляд літератури щодо наявності морфологічних змін показників кровотворення при інфекції SARS-CoV-2 та виявити їх прогностичне значення для визначення перебігу захворювання.*
Результати та висновки. *У всіх випадках інфекції SARS-CoV-2 спостерігалися морфологічні зміни, принаймні в одній лінії клітин крові. Найпоширенішими були ядерні та цитоплазматичні порушення нейтрофілів: гіпогрануляція та гіпо/гіперсегментація ядер нейтрофілів, часто з токсичною зернистістю. Типові зміни морфології лімфоцитів включають моноцитоїдні, лімфоплазмоцитоїдні, гранулярні та атипові клітини з ядерцями. Прогностично несприятливими морфологічними ознаками в периферичному мазку крові є гігантські нейтрофіли та їх токсична зернистість, плазмоцитизація лімфоцитів, динамічне зменшення зернистих і аномальних лімфоцитів і моноцитів. Низька кількість лімфоцитів та їх субпопуляцій*

асоціюється з тяжкою клінічною картиною та несприятливим результатом захворювання на COVID-19, що свідчить про доцільність їх імунофенотипічної оцінки та моніторингу. Виявлення та серійний моніторинг запальних моноцитів за допомогою проточної цитометрії може бути цінним для прогнозування перебігу та вибору адекватної терапії інфекції SARS-CoV-2. Крім того, було показано, що збільшення ширини розподілу еритроцитів має прогностичне значення.

A literature review on the management of patients with COVID-19 disease reveals that it is a multisystem disorder that also affects the hematopoietic system, leading to the appearance of morphological changes in blood cells in patients with SARS-CoV-2 infection.

The types of morphological changes in the complete blood count, along with other laboratory parameters, can help determine the severity of the condition and have prognostic value for the patient's survival. Identifying prognostic markers can aid in clinical decision-making. Peripheral blood (PB) smear examination is a routine and simple procedure that can be performed at any medical institution. However, data on morphological changes in PB cells during Covid-19 are still insufficient. Available research results mainly focus on quantitative indicators [1], while structural cellular changes reflect the depth of hematopoietic disorders. Therefore, it is relevant to identify the features and patterns of these changes, taking into account the severity of the clinical presentation of COVID-19, and establish their prognostic significance.

Aim. To review the literature on the presence of morphological changes in hematopoietic parameters in the case of SARS-CoV-2 infection, taking into account the clinical picture of the disease course.

Main body. L. Florian and co-authors presented a case study of a 39-year-old woman with typical manifestations of COVID-19. Among the quantitative indicators of the complete blood count, the following were observed: mild anemia, severe leukopenia with a predominance of neutrophils in the white blood cell differential (84%), as well as occasional blastoid cells. The bone marrow examination showed a myeloid left shift, a predominance of immature neutrophils, and up to 30% of atypical cells. The blastoid cells were dysplastic immature neutrophils. When staining blood smears with Wright-Giemsa, neutrophilic granulocytes with hypogranulation of the cytoplasm and a hyposegmented nucleus were observed. After six months of monitoring the blood test, the leukocyte count returned to normal, and their morphological atypia disappeared [2].

Other authors have reported similar morphological abnormalities, specifically the presence of dysplastic neutrophils with a myeloid left shift in SARS-CoV-2 infections [3, 4]. The most significant morphological changes in the peripheral blood smear are neutrophils with clumpy chromatin, multiple abnormal nuclear shapes, pseudo-Pelger-Huet deformity, and smudged neutrophils [5].

Acquired Pelger-Huth anomaly was noted in all cases of COVID-19, affecting more than 5% of granulocytes in most cases. Monolobed neutrophils were rare in cases of COVID-19 [6].

Yarali Neşe et al presented severe nonspecific dysplastic changes in granulocytes and platelets in patients with COVID-19, along with lymphopenia and reactive lymphocytosis [7]. Morphological changes in neutrophils, such as nucleus hypersegmentation (with up to eight segments) and toxic granulation, are observed in 75% of cases [8]. The number of giant neutrophils and toxic granulations/Döhle bodies is elevated in severe COVID-19 [9].

With COVID-19 infection, neutrophils with abnormal nuclear shapes in the form of ring-shaped and pi-shaped are also found [5]. A. Singh et al described fetus-like C-shaped nuclei with nuclear projections, which were named COVID nuclei [10]. Other authors report the appearance in the PB smear of apoptotic cells with liquefied nuclear chromatin and granular or dark blue cytoplasm, resembling polymorphs with nuclear fragmentation, the frequent presence of immature granulocytes in the form of small promyelocytes, myelocytes, or metamyelocytes. There are also reactive large atypical monocytes with an abnormal nucleus shape and cytoplasmic vacuolisation [4, 11].

The reported circulating granulocytes with cytoplasmic and nuclear morphological abnormalities usually appear before an increase in reactive lymphocytes in COVID-19 infection [12, 13]. It is hypothesized that granulocyte dysplasia may be linked to increased activity of pro-inflammatory cytokines in these patients due to infection [2, 14]. The inhibitory effect of cytokines from virus-infected cells on myeloid bone marrow cells was also revealed [7]. High levels of interleukin-6 (IL-6) were found to be correlated with pyknotic cells (p=0.003) [15].

If larger studies confirm these morphological changes in PB cells, they could potentially serve as a basis for diagnosing COVID-19 in the absence of a PCR test.

In the literature, there are reports of dysplastic cells appearing not only in the myeloid but also in the lymphocytic series during coronavirus infection.

Samuel E. Weinberg et al reported the presence of medium to large atypical lymphocytes with loosely condensed chromatin, and moderate to deep basophilic cytoplasm on the background of lymphopenia or a lower lymphocyte norm in the analysis of peripheral blood in hospitalized COVID-19 patients. In some patients, the same lymphocytes were found in bronchial alveolar lavage smears. However, their percentage in total lymphocyte count did not correlate with disease severity [16].

The most common finding on a peripheral blood smear in COVID-19 patients is lymphopenia with reactive lymphocytes, some of which appear as monocytoid or lymphoplasmacytoid cells [17]. A. Singh et al described the presence of large granular lymphocytes with round or jagged nuclei, condensed chromatin, some of them with

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prominent nucleoli, along with abundant pale blue cytoplasm with distinct azurophilic granules. These cells are likely to be natural killer/cytotoxic T-lymphocytes. The formation of apoptotic bodies and cytoplasmic follicles was observed in some lymphocytes [10].

The literature also describes large atypical, bizarre mononuclear cells, which are 2-3 times larger than erythrocytes and have irregular nuclear membranes, dense chromatin, sparse or moderate cytoplasm, and a small number of cytoplasmic granules and vacuoles in SARS-CoV-2 infection [18].

A study by E. Schapkaitz et al. showed that 57.8% of patients with Covid-19 had atypical lymphocytes in peripheral blood [3]. G. Kaur reported the presence of lymphocytes with abundant blue cytoplasm and/or plasmacytoid lymphocytes [5]. In patients with clinically manifested COVID-19, plasmacytoid lymphocytes were statistically significantly more common (p<0.05) [6, 19]. D. Foldes and co-authors believe that monitoring of plasmacytoid lymphocytes confirms the provisional clinical diagnosis of this condition [19].

According to an immunophenotypic study by Y. Liu et al, T-lymphocyte subpopulations have prognostic significance for the course of SARS-CoV-2 infection. There was a negative linear correlation between viral load and the number of CD4+ and CD8+ T-lymphocytes, but a strong direct relationship with disease severity [20].

Y.M. Akçabelen et al. found numerous giant platelets and vacuolated monocytes in a PB smear, along with dysplastic neutrophils, in children with COVID-19 [21]. Platelet morphological abnormalities have also been described in this disease, both in patients with thrombocytosis and in patients with thrombocytopenia. These morphological changes include the presence of giant platelets, usually hyperchromic, vacuolated, and some with pseudopedicles [22, 23]. G. Kaur and co-authors draw attention to the importance of platelet clumping with a normal count in most COVID-19 patients [5].

The literature reports on erythropoietic changes in COVID-19 infection, which may play an important role in disease progression [24, 25]. G. Kaur et al describe the morphology of red blood cells as mostly normocytic and normochromic, with some cells having nuclei and coarse basophilic stippling [5]. The red cell distribution width is much higher in severe cases of the disease with high mortality [9, 24, 25].

A. Berzuini et al describe morphological abnormalities of erythrocytes in blood smears, such as high percentages of stomatocytes and knizocytes, which are rarely found in other types of anemia [26]. T. Thomas et al.'s studies revealed changes in the N-terminal cytosolic domain of band 3 (AE1), which suggest a decrease in the ability of erythrocytes in Covid-19 patients to respond to environmental variations in hemoglobin oxygen saturation/oxidant stress. Increased oxidation of structural proteins and disorder of membrane lipid homeostasis have been found, which may alter erythrocyte elasticity, potentially contributing to the thromboembolic complications seen in severe Covid-19 disease [27]. Further research is needed into the role of erythrocytes in

the pathophysiology of SARS-CoV-2 infection, as well as pathways for reversing erythrocyte dysfunction. Therapeutic intervention may include inhibition of reactive oxygen species production and/or antioxidant therapy [28]. A leukoerythroblastic blood picture is described on rare occasions [29].

The excessive activation of the macrophage system with the development of a cytokine storm and subsequent acute lung injury leading to acute respiratory distress syndrome is a dangerous consequence of SARS-CoV-2 infection. Therefore, it is of great clinical importance to recognize it in the early stages of development in patients at the highest risk for timely therapy correction. In this regard, the results of studies by D. Zhang et al are worth attention. The analysis of blood parameters between 34 patients with COVID-19 and a group of healthy individuals, despite the absence of significant differences in the count of monocytes, which are progenitors of macrophages in tissues, revealed substantial morphological and functional differences in the aforementioned groups. More pronounced changes in monocytes were seen in patients requiring long-term hospitalization and treatment in the intensive care unit (ICU). Covid-19 patients had large monocytes, which were distinct on forward scatter analysis by routine flow cytometry (FSC high). These monocytes had features of a mixed population of M1/M2 macrophages with higher expression of CD80+ and CD206+ compared to other monocytes with low FSC levels, and secreted higher levels of IL-6, IL-10, and TNF-α when compared with the normal controls [4].

The authors H. Gabr and colleagues, in addition to the previous reports, described pyknotic and destroyed cells, pseudo-Pelger-Huet nuclei of neutrophils, abnormal lymphocytes, and monocytes, and the presence of a leukoerythroblastic reaction in a peripheral blood smear in their examination of 113 COVID-19 patients and 50 controls without COVID-19. Some of the disease cases had unfavorable outcomes [15].

I. Berber and colleagues found, in their examination of 50 patients with SARS-CoV-2 infection and 30 healthy individuals, a significantly higher count of neutrophils with Pelger-Huet anomaly in infected individuals compared to the number of mature lymphocytes, along with a decrease in the number of segmented neutrophils and eosinophils. These differences were related to the severity of the disease. Meanwhile, a high initial percentage of mature lymphocytes and monocytes with vacuoles at the time of diagnosis may be prognostically favorable for reducing the length of hospital stay [30].

After examining 50 COVID-19 patients, S. Bahadur and colleagues reported the most frequent statistically significant changes in peripheral blood smears: hypolobization of neutrophil nuclei and the presence of toxic granules in them, the presence of atypical granules with nucleolar prominences in lymphocytes, cytoplasmic granulation with clumped nuclear chromatin in monocytes, giant platelets on the background of thrombocytopenia, and normocytic normochromic anemia. The authors did not find any relationship between the severity of the clinical

condition and the viral load size, as well as between the morphological changes in peripheral blood and the viral load [31].

Y. Horiuchi et al., in their study of 38 healthy individuals and 40 COVID-19 patients, found that in addition to more pronounced quantitative changes in PB parameters in severe patients compared to mild cases (anemia, lymphopenia, leukocytosis (p<0.001)), there were also morphological cell disorders. The granular lymphocyte count was normal or higher in mild cases and significantly lower in fatal cases. A transient increase in granular lymphocyte count has been associated with survival in patients with severe infections [9].

O. Pozdnyakova et al. conducted a study on 90 patients with coronavirus infection and 30 intensive care patients with other diseases and a negative result for COVID-19. All patients with viral infection demonstrated pronounced quantitative and morphological changes in leukocytes. Abnormal leukocyte morphology was most pronounced in monocytes and lymphocytes in mild cases and disappeared as the disease progressed. Significant differences in cell morphology were observed between COVID-19-positive and COVID-19-negative ICU patients, indicating a role for coronavirus in their occurrence. In severe acute respiratory syndrome, there was a higher RNA content in monocytes, lower content in lymphocytes, and the presence of smaller hypogranular neutrophils [32].

Similar studies in comparable groups of patients were conducted by S. Jain et al. compared to the COVID-19 negative group (consisting of 32 healthy individuals), the COVID-19 positive group (consisting of 80 individuals) showed significantly more pronounced myeloid left shift and a higher frequency of Döhle bodies, acquired pseudo-Pelger-Huët anomaly, ring-shaped and monolobed neutrophils, and plasmacytoid lymphocytes in the analysis of PB. The greater left shift, total white blood cell count with ring-shaped neutrophils, the number of monocytes with vacuolation, and large granular lymphocytes in COVID-19-positive ICU patients were statistically significantly higher compared to milder non-ICU cases. These parameters have become highly sensitive markers of disease severity [33].

In patients with severe COVID-19, bone marrow aspirate shows histiocytic proliferation with hemophagocytosis, which may indicate a poor clinical outcome [17, 34, 35]. According to A. Rahman et al, COVID-19 may predispose to hemophagocytic lymphohistiocytosis through activation of the IL-1/IL-6 pathway, including the overproduction of IL-1β by macrophages. The authors also reported an increase in pleomorphic megakaryocytes, plasma cells, and macrophages in the bone marrow [36].

The morphology of blood cells may be abnormal in myelodysplastic syndrome, as well as in various non-clonal disorders, such as infections, autoimmune diseases, malnutrition, drug or toxin exposure. It has been observed that the inhibitory effect of cytokines from virus-infected cells on hematopoiesis can also cause myelodysplastic changes [37], which is seen in cases of SARS-CoV-2 infection.

Conclusion

1. In almost all cases of manifestation of COVID-19, one, two, or three blood cell lineages have varying numbers of morphological changes.

2. The most common were nuclear and cytoplasmic disorders of neutrophils, such as hypogranulation and hypo/hypersegmentation of neutrophil nuclei, often with toxogenic stippling.

3. Typical changes in lymphocyte morphology include monocytoid, lymphoplasmacytoid, granular, and atypical cells with nucleoli.

4. Prognostically unfavorable morphological signs in the peripheral blood smear include giant neutrophils and their toxic granulation, plasmacytization of lymphocytes, a dynamic decrease in granular and abnormal lymphocytes and monocytes.

5. A low count of lymphocytes and their subpopulations is associated with a severe clinical presentation and an unfavorable outcome of COVID-19 disease, which suggests the feasibility of their immunophenotypic evaluation and monitoring.

6. The detection and serial monitoring of inflammatory monocytes using flow cytometry may be valuable in predicting the course and choosing adequate therapy for SARS-CoV-2 infection.

7. An increase in red cell distribution width is associated with dyserythropoiesis and has prognostic importance.

Therefore, a complete blood count with a comprehensive analysis of quantitative and morphological data should be performed on each newly diagnosed hospitalized patient with COVID-19, as it has the potential to predict the course of the disease.

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